UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,936	11/07/2001	Olle Korsgren	KORSGREN-1	9165

1444 7590 03/31/2005

BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 03/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,936	KORSGREN ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 2, 2004 has been entered.

The amendment filed 2 March 2004 has been received and entered. Claim 4 has been amended and claims 12 and 13 have been added. Claims 1-13 are pending to which the following grounds of rejection are or remain applicable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Claims 1, 4, and 10 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant has added a proviso that

the isolated islets are not artificially encapsulated. This is new matter since it is not described in the instant specification.

The remaining claims, read in light of the amendatory material of claims 1, 4 and 10, would also be subject to the new matter issue as containing within their scope, the proviso language.

Claims 1, 2, 4-8 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reduction of clotting in a patient, it does not reasonably provide enablement for preventing clotting. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims as directed to transplanting unencapsulated islet cells and in the absence of appropriate immunosuppression therapy.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: Claim 1 is drawn to a method of transplanting unencapsulated insulin producing cells to a patient suffering from insulin dependent diabetes mellitus (IDDM) comprising modifying isolated islet cells by irreversible adsorption with a clotting preventing agent. The nature of the

invention is extremely complex in that it encompasses the actual prevention of blood clots such that the subject treated in the manner described in the claims would not have a clot as well as the issue of transplant rejection. The examples in the specification do not demonstrate how or by what means the issue is obviated[1].

Breath of the Claims: The complex of nature of the claim is greatly exacerbated by breath of the claim. The claims encompass prevention of a clot, which have potentially many different causes[2]. Each of these states of clotting, both as a natural process and in a disease state may or may not be addressed by the method recited in the claims, i.e., preventing clotting in unencapsulated islet cells.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed clotting preventing agent to a patient in order to actually prevent clotting is minimal. All of the guidance provided by the

---

[1] See Diabetes Dateline, enclosed herein that states that past experience has shown that at least two hurdles must be overcome before islet transplantation can be developed into a viable curative therapy for type-1 diabetes. One hurdle is the immune response all patients generate against transplanted organs or tissues. Another is that people with type-1 diabetes have the disease because their immune system has already destroyed their islet cells. Research suggests that if islets are transplanted into patients with type-1 diabetes, not only are those islets subjected to the usual immune response, but the autoimmune response is also reactivated.

[2] Blood clotting is a natural process in which blood cells and fibrin strands clump together to stop bleeding after a blood vessel has been injured. Eventually the clot will form a protective scab over a healing wound. If the body did not have the ability to clot blood, then people would bleed to death after even a minor cut. Sometimes blood clots form even when a person has not been injured. Although most blood clots tend to dissolve on their own with no long-term problems, there are situations in which blood clots can cause medical problems. Blood clots become dangerous when they block blood flow through an artery or vein. When a blood clot blocks blood flow to an artery in the heart or

specification is directed towards inhibition of thrombus formation on the isolated islet cells and does not demonstrate nor explain elimination or minimizing transplant rejection issues. Note that the claims do not require use of immunosuppressants nor set forth in the specification how transplant rejection of heterologous cells would escape from an adverse immune reaction.

Working Examples: All of the working examples provided by the specification are directed toward reduced clotting rather than prevention of clotting in isolated islets (see page 6, first full paragraph) and none demonstrate neither eliminating nor minimizing transplant rejection or effective immune tolerance[3].

State of the Art: While the state of the art is relatively high with regard to **clot reduction or inhibition**, the state of the art with regard to absolute **prevention** of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to absolutely **prevent** development of clotting, both natural or in disease states Also, regarding the state of the art with regard to transplantation in the absence of immunosuppression, there do not appear to be any examples or teachings. See footnotes 1 and 3.

---

brain, a heart attack or stroke may result. Blood clots can also block veins and arteries throughout the body, causing diseases that range from varicose veins to life-threatening pulmonary embolism

[3] See Preliminary Results of ITN Multicenter Islet Transplant Trial Confirm Potential Patient Benefits, Underscore Steep Learning Curve, see page 2, 2nd paragraph, wherein it is recited regarding transplants if islet cells, "there was no clear explanation for graft failure in six of the patients enrolled in the trial. In

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual **prevention** of clotting in a patient with the clotting preventing agents recited makes practicing the claimed invention unpredictable in terms of prevention of clotting. The art is predictive of immune rejection of the invention as currently claimed.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, clot preventing agent dosage, duration of treatment, route and frequency of administration, etc. and appropriate animal model system for one of the claimed clot prevention agents and test the combination in the model system to determine whether or not the combination is effective for **prevention** of clotting. If unsuccessful, which is likely, given the lack of significant guidance from the specification or prior art with regard to absolute prevention of clotting, one of skill in the art would have to then either envision a modification of the clot prevention agent, clot prevention dosage, duration of treatment, route of administration, frequency of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance from the specification of prior art regarding prevention

---

some cases, physicians were unable to achieve adequate levels of immunosuppression to prevent

of clots, the entire, unpredictable process would have to be repeated until successful. Given the issue of immune rejection coupled with lack of preceding factors, it is readily apparent that the specification fails to explain how to overcome the issues. The makes experimentation undue as well as unpredictable. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of clots in a patient by administration of one of the clot prevention agents. Therefore, a method of **preventing** in a patient clots by administering the clot preventing agents is not considered to be enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 12 and 13 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 12 and 13 recites the limitation "said isolated islets" in line 5 of the claim. There is insufficient antecedent basis for this limitation in the claim because the claim is drawn to the method comprising transplantation of insulin producing cells in the form of isolating islets.

---

rejection.

Claims 2, 5, 6, 7, 9 recite the limitation "the preventing agent". There is insufficient antecedent basis for this limitation in the claim because the claim depends from claim 1 which recites "a clotting preventing agent".

The remaining claims are indefinite to the extent that they read on the rejected base claims.

The rejection made in paper number 5 over Wagner et al. under 35 U.S.C. §102(b) is maintained and is hereby repeated below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-4 and 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Wagner et al. DE 196 23 440 A 1.

Wagner et al. teach method of use of anticoagulants such as heparin, hirudin and Marcumar and derivatives thereof in connection with transplantation of insulin producing cells such as islets of Langerhans (see claim 8). The cells may be in the form of microencapsulated islets (see figure 1 and claim 10) and where immunosuppression can be an issue, see "Islet Transplant Info" that teaches that immunosuppression and/or appropriate drugs, such as Zenapax should be used to address the issue.

Applicant asserts that Wagner teaches microencapsules used in transplantation surgery. The abstract for Wagner et al. teach that the immobilized material is insulin, proinsulin and/or organ cells of xenogenic or autogenic origin (islets of Langerhans, etc.) and the system contains an agent to inhibit or suppress blood agglutination, agglomeration antagonists, heparin, hirudin, marcumar and their derivatives. Wagner

discloses that the islets *may* be microencapsulated. Additionally, if the cells are microencapsulated, they are first mixed with the anticoagulant material, thus anticipated the claims of the instant application. An English language translation of the Wagner et al. patent is enclosed.

The rejection made in paper number 5 over Lenchow et al. under 35 U.S.C. §102(b) is maintained and is hereby repeated below.

Claims 1 and 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Lenschow et al. (Science 7 Aug 1992 Vol. 257 ages 789-792).

Lenchow et al. teach antigen-specific T cell activation depends on cell receptor-ligand interaction and co-stimulatory signals generated when accessory molecules bind to their ligands, such as CD28 to the B7 molecule. A soluble fusion protein of human CTLA-4 and the immunoglobulin G1Fc region binds to human and murine B7 with high avidity and blocks T cell activation in vitro. This CTLA4Ig therapy blocked human pancreatic islet rejection in mice by directly affecting T cell recognition of $B7^+$ antigen-presenting cells and inducing long-term donor-specific tolerance (see abstract). Diabetic mice were grafted under the kidney capsule and treatment was started immediately after surgery and survival of the islet grafts were monitored (page 790, column 1, paragraph 2. Treatment resulted in 100% of the animals maintaining normal islet function throughout the experiment with no signs of a rejection crisis (page 790, column 2, paragraph 1). Additionally, note that there is no provision in the instant claims that deals with the immunosuppression issue, without which, the transplanted islet cells would be rejected (see Islet Transplant Info).

Applicant asserts that while Lenchow does describe the use of human islets for transplantation, and additionally uses an immunoglobulin G1Fc, that Lenchow does not address the coagulation process. This process is considered to be inherent. Since the immunoglobulin G1Fc is a clotting preventing agent, and it is administered with the islet cells, it anticipates the claims.

The rejection made in paper number 5 over Soon-Shiong et al. under 35 U.S.C. §102(b) is maintained and is hereby repeated below.

Claims 1-4, 10 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Soon-Shiong et al. U.S. 5,705,270 A.

Soon-Shiong et al. teach microcapsules containing biological material such as islet of Langerhans cells coated with polymerizable materials (see abstract, see also claim 3). The microcapsules are covalently linked with heparin (see claim 5). Soon-Shiong et al. teach encapsulation of islets of Langerhans for treatment of diabetes (column 4, lines 1-4) to prevent the detrimental effects of capsule instability on the encapsulated biologically active material e.g. loss of immunoprotection for the encapsulated material is minimized (column 3, lines 61-66). Additionally, note that there is no provision in the instant claims that deals with the immunosuppression issue, without which, the transplanted islet cells would be rejected (see Islet Transplant Info).

Applicant asserts that the instant invention does not involve and applicants do not claim microcapsules as disclosed by Soon-Shiong et al. However, upon examination of the instant specification, applicant describes immobilizing heparin according to a method developed by Corline Systems AB disclosed in WO 93/05793

(page 4 of the instant specification). The heparin in WO 93/05793 appears to be immobilized (conjugated) with a polymer comprising a substantially straight-chained organic homo or hetero polymer having a number of functional groups distributed along the polymer backbone chain via which groups at least about 20 molecules (see page 7 of WO 93/05793). While applicant asserts that the heparin is not in microcapsules, it appears that it is similarly coated and as such, must form micro (or macro) capsules if applicant has followed the technique of Corline Systems AB as recited in applicants specification.

The rejection made in paper number 5 over Soon-Shiong et al. under 35 U.S.C. §103(a) is maintained and is hereby repeated.

Applicant asserts that Soon-Shiong does not disclose use of a clot-preventing agent to produce a drug for transplantation of insulin producing cells in the form of isolated islets to patients with insulin dependent diabetes mellitus wherein the inhibitor is an inhibitor of platelet activation. The reference discloses therapeutic applications such as the encapsulation of islets of Langerhans for the treatment of diabetes (column 3, line 65 to column 4, line 1). It would have been obvious to one of skill in the art to substitute an agent that inhibits platelet activation for an agent such as heparin that inhibits thrombin since the end result of both agents is to inhibit a blood clot. It is prima facie obvious to substitute equivalents, motivated by the reasonable expectation that the respective species will behave in a comparable manner or give comparable results in comparable circumstances. *In re Ruff* 118 USPQ 343; *In re Jezel* 158 USPQ 99; the

express suggestion to substitute one equivalent for another need not be present to render the substitution obvious. *In re Font*, 213 USPQ 532.

Response to Declaration under 37 CFR 1.132

The Declaration under 37 CFR 1.132 filed 2 March 2004 is insufficient to overcome the rejection of claims 1-11 based upon the stated prior art as set forth in the last Office action because: while applicant maintains that the cells are **not artificially encapsulated** in the independent claims, there is no support in the instant specification for such a claim. As stated in the advisory action dated 12/17/2003, applicant's disclosure relies on Corline Systems AB wherein the heparin is immobilized (conjugated) with a polymer having a substantially straight chained organic homo or hetero polymer. This does not appear to be a "non-artificial" process as claimed. Applicant has not clearly pointed out the novelty of the instant invention as represented by the instant claims.

Response to Arguments

In response to applicant's assertion that "none of the prior art references anticipate applicants' claims and no rejections have been imposed under 35 USC §103 and applicants agree that the prior art does not make obvious any applicants' claims", the examiner wishes to direct applicant to the office action dated 26 February 2003 and the 35 USC 103 rejections contained therein and still maintained.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Thursday from 9:00 A.M. - 3:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Donna Jagoe
Patent Examiner
Art Unit 1614

03/19/2005

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600